IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. MBHB00-210)

In the Application of:

Arminjon *et al.*

Serial No.: 09/508,570

Filing Date: May 23, 2000

For: Multivalent Vaccines

Examiner: S. Brown

Group Art Unit: 1648

APPEAL BRIEF

Commissioner for Patents
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Real Party in Interest

The real party in interest is Aventis Pasteur.

Related Appeals and Interferences

There are no related appeals or interferences.

Status of Claims

Claims 21-27 and 29-38 are pending and are under final rejection. A copy of these claims is attached hereto in the Appendix.

Status of Amendments

No amendments were filed after final rejection.

Summary of the Invention

The present invention comprises a combination or multivalent vaccine composition containing a plurality of vaccine components suitable for the prevention, amelioration, or treatment of multiple disease states by providing seroprotection against the disease corresponding to each of the vaccine components. P. 8, l. 20 *et seq.* The invention also comprises methods of making such compositions. *Id.* The multivalent immunogenic composition (and methods of making them) of the claims on appeal comprises pertussis toxoid and filamentous haemagluttinin, in purified form, tetanus toxoid, diphtheria toxoid, inactivated poliovirus, and a conjugate of a carrier molecule and a capsular polysaccharide of Haemophilus influenzae type b. *See* claims in Appendix. In the methods and compositions of the present invention, the immunogenic composition is formulated in a single

composition for *in vivo* administration to the host such that the immunogenicity of individual components is not impaired by other individual components of the composition. P. 8, l. 36 *et seq.* The immunogenic compositions further comprise an adjuvant, particularly aluminum salts such as aluminum hydroxide or aluminum phosphate. P. 9, ll. 9-10. Various components are adsorbed onto the aluminum adjuvant before being admixed with the other components. P. 16, l. 23 *et seq.*

Extensive clinical trials described demonstrate that the multivalent immunological compositions of the present invention are safe and efficacious for conferring protection against a broad range of pathogens. P. 25, ll. 18-20. These results are surprising insofar as mixtures of numerous vaccine components may have been expected to contribute to the well-recognized phenomena of antigenic competition or interference, whereby certain vaccine components which would be capable of conferring seroprotection when introduced individually into an immuno-competent host become less effective when introduced in combination with other antigens. P. 25. ll. 22-25. Thus, the vaccines of the present invention simplify the immunization process and greatly minimize the number of separate immunizations needed to protect pediatric patients from infection. P. 25. ll. 26 *et seq.*

Issues

1. Whether claims 21-27 and 29-38 are obvious under 35 U.S.C. § 103(a) over Petre *et al.* (WO 93/24148) in view of Arminjon AU 708777.

Grouping of the Claims

All claims stand or fall together.

Argument

The claims are rejected under 35 USC § 103(a) as being obvious over Petre *et al.* (WO 93/24148) in view of Arminjon *et al.* (AU 708777 or WO 96/37222). For the following reasons, the applicants respectfully traverse.

The cited art, alone and in combination, fails to teach or suggest each and every limitation of the claims on appeal, and it fails to provide the ordinary artisan with a reasonable expectation of success.

The cited art fails to teach or suggest a vaccine composition, together with an aluminum salt adjuvant, made by combining the valencies of the present claims, *i.e.*,

1) pertussis toxoid
2) filamentous haemagluttinin,

3) tetanus toxoid,

4) diphtheria toxoid,

5) inactivated poliovirus, and

6) a conjugate of a carrier molecule and a capsular polysaccharide of Haemophilus influenzae type b

according to the method recited in claim 21.

The Office has failed to clearly and with particularity identify the teachings or suggestions in the prior art to make the presently claimed methods and compositions comprising each of the recited antigens as required. *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed"). A general motivation is legally insufficient. *In re Deuel*, 34 U.S.P.Q.2d 1210, 1216 (Fed. Cir. 1995) ("A general incentive does not make obvious a particular result..."); *In re Obukowicz*, 27 U.S.P.Q.2d, 1063, 1065 (Bd. Pat. App. Int. 1992) (Prior art "that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it . . . does not make the invention obvious."). The applicants respectfully submit that the cited art does not teach or suggest the particular methods and compositions comprising the particular antigens now being claimed.

Furthermore, the ordinary artisan would not have a reasonable expectation of successfully combining all of the antigens of the present claims to arrive at a composition having efficacy for each of its constituents. As described on page 7 of the specification, results obtained with combination vaccines comprising antigens of pertussis, diphtheria, tetanus, and Hib (PRP or PRP-T) have been mixed, with some reporting decreases in immune response for combinations of antigens and others reporting increases. The uncertainty the ordinary artisan faces when combining antigens has been acknowledged in the art. Eskola, *J. Infectious* Diseases **174(Suppl 3)**:S302-5 (1996) (Exhibit A), entitled, "Analysis of *Haemophilus* influenzae Type B Conjugate and Diphtheria-Tetanus-Pertussis Combination Vaccines," states in the introduction:

> Combined vaccines cannot, however, be made by simply mixing vaccines in the same syringe. One must take into consideration all constituents, including stabilizers, preservatives, and adjuvants, and their relative properties and potential chemical and ciologic interactions.

p. S302, col. 1. And in the section entitled, "Implications for the Future," (pp. S304-S305), Eskola states:

> In the next few years, data from vaccine trials will affect the development of combined vaccines. Evidence of the protective efficacy and clinical usefulness of Pa [acellular pertussis] vaccines will be available soon. National vaccination programs will probably start using DTPa instead of DTPw [whole cell pertussis], and new combined vaccines, such as DTPa-Hib and DTPa-IPV-Hib, may become available.
>
> From experience with DTPw-Hib combinations, one could expect interference between Hib, diphtheria, tetanus, and pertussis antigens in the new Dtpa-Hib combined vaccines. The clinical significance of this interference must be considered carefully.

Thus, the art recognizes the obstacles faced by the ordinary artisan when preparing a multivalent vaccine. Due to the phenomenon of antigenic competition (wherein following administration of several antigens the immune response to one or more of them is suppressed or diminished), one cannot merely select any random combination of antigens with the expectation that a vaccine comprising them will confer seroprotection against the diseases associated with each.

Moreover, as the number of antigens in a composition increases, the likelihood of antigenic competition increases, as each antigen may negatively compete with every other antigen present in the composition. Consequently, *a priori* one cannot know with a reasonable degree of certainty whether a particular combination of antigens will exhibit antigenic competition. There is nothing in Petre *et al.* and/or Arminjon *et al.* addressing the issue of antigenic competition and, therefore, nothing in either of these references that would imbue the ordinary artisan with a reasonable expectation that the particular compositions antigens made by the method now being claimed would not exhibit antigenic competition.

As noted above in the Summary of the Invention section, extensive clinical trials described in the specification demonstrate that the multivalent immunological compositions of the present invention are safe and efficacious for conferring protection against a broad range of pathogens. P. 25, ll. 18-20. As further stated in the specification (p. 25. ll. 22-25), "These results are surprising insofar as mixtures of numerous vaccine components may have been expected to contribute to the well-recognized phenomena of antigenic competition or interference, whereby certain vaccine components that would be capable of conferring seroprotection when introduced individually into an immunocompetent host become less effective when introduced in combination with other antigens."

Such results as observed by the applicants for the presently claimed methods and compositions are further evidence of their non-obviousness *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995) ("One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.")

In conclusion, because (a) the prior art fails to provide a particularized teaching or suggestion to make the presently claimed methods and compositions comprising each of the recited antigens, (b) the prior art fails to imbue the ordinary artisan with a reasonable expectation of success (*i.e.*, that the multivalent compositions of the claims would not exhibit antigenic competition), and (c) the lack of antigenic competition was unexpected, the presently claims cannot be obvious. Accordingly, the Applicants respect-fully request reconsideration and withdrawal of this rejection.

Respectfully submitted,

Date: November 18, 2003

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APPENDIX

CLAIMS ON APPEAL FOR APPLICATION SERIAL NO. 09/508,570

21. A method for preparing a stabilized multi-component vaccine, the method comprising mixing at least:

a) pertussis toxoid and filamentous hemagglutinin in purified form,

b) tetanus toxoid,

c) diphtheria toxoid,

d) inactivated polio virus,

e) a conjugate of a carrier molecule selected from tetanus toxoid and diphtheria toxoid and a capsular polysaccharide of *Haemophilus influenzae* type B, and

f) an aluminum salt,

wherein tetanus toxoid and diphtheria toxoid are adsorbed onto the aluminum salt before being mixed with the other components and the conjugate is prepared in a phosphate buffer solution before being mixed with the other components.

22. The method according to claim 21, wherein pertussis toxoid and filamentous hemagglutinin in purified form are adsorbed onto an aluminum salt before being mixed with the other components.

23. The method according to claim 21, wherein inactivated polio virus is mixed with the other components without being adsorbed onto an aluminum salt.

24. The method according to claim 21, wherein the aluminum salt is selected from a group consisting of aluminum hydroxide and aluminum phosphate.

25. The method according to claim 21, further comprising adding hepatitis B surface antigen adsorbed onto an aluminum salt before being mixed with the other components.

26. The method according to claim 21, wherein mixing is conducted in the following order:

a) adsorbing tetanus toxoid and diphtheria onto aluminum hydroxide,

b) adsorbing pertussis toxoid and filamentous hemagglutinin in purified form onto an aluminum salt,

c) mixing the components obtained in a) with those obtained in b),

d) adding inactivated polio virus,

e) adding a phosphate buffer solution of a conjugate of a carrier molecule selected from tetanus toxoid and diphtheria toxoid and a capsular polysaccharide of *Haemophilus influenzae* type B.

27. A method according to claim 25 wherein mixing is conducted in the following order:

a) adsorbing tetanus toxoid and diphtheria onto aluminum hydroxide,

b) adsorbing pertussis toxoid and filamentous hemagglutinin in purified form onto an aluminum salt,

c) mixing the components obtained in a) with those obtained in b),

d) adding inactivated poliovirus after c),

e) adding hepatitis B surface antigen previously adsorbed onto an aluminum salt after d),

f) adding a phosphate buffer solution of a conjugate of a carrier molecule selected from tetanus toxoid and diphtheria toxoid and a capsular polysaccharide of *Haemophilus influenzae* type B after e).

29. The method according to claim 25, wherein hepatitis B surface antigen previously adsorbed onto aluminum salt is added separately from the other components within a dual chamber syringe.

30. A multi-component vaccine obtained by the method according to claim 21.

31. The multi-component vaccine according to claim 30, wherein the amounts of pertussis toxoid and filamentous hemagglutinin are between 5 and 30 µg in a single dose of said multi-component vaccine.

32. The multi-component vaccine according to claim 30, wherein the amounts of diphtheria toxoid and tetanus toxoid are between 5 and 30 LF in a single dose of said multi-component vaccine.

33. The multi-component vaccine according to claim 30 wherein the amounts of the different polioviruses are

a) between 20 and 50 D antigen units of poliovirus type 1,

b) between 4 and 10 D antigen units of poliovirus type 2, and

c) between 8 and 40 antigen units of poliovirus type 3,

in a single dose of said multi-component vaccine.

34. A multi-component vaccine obtained by the method of claim 27, wherein the composition of said vaccine comprises per 0.5 ml dose:

a) 25 µg pertussis toxoid;
b) 25 µg filamentous hemagglutinin;
c) 30 LF diphtheria toxoid;
d) 10 Lf tetanus toxoid;
e) 40 D antigen units poliovirus type 1;
f) 8 D antigen units poliovirus type 2;
g) 32 D antigen units poliovirus type 3;
h) 10 µg Haemophilus influenzae type B polysaccharide covalently bound to 20 µg tetanus toxoid; and
i) 5 µg hepatitis B surface antigen.

35. The multi-component vaccine according to claim 30, wherein the composition of said vaccine comprises per 0.5 ml dose:

a) 25 µg pertussis toxoid;
b) 25 µg filamentous hemagglutinin;
c) 30 LF diphtheria toxoid;
d) 10 Lf tetanus toxoid;
e) 40 D antigen units poliovirus type 1;
f) 8 D antigen units poliovirus type 2;
g) 32 D antigen units poliovirus type 3;
h) 10 µg Haemophilus influenzae type B polysaccharide covalently bound to 20 µg tetanus toxoid;
i) 5 µg hepatitis B surface antigen;
j) 20 µMoles phosphates;
k) 5 µMoles carbonates;
l) 0.125 ml of 50 mM tris buffer; and
m) 0.356 mg aluminum salt.

36. A method for conferring protection in a host against disease caused by *Bordetella pertussis*, *Clostridium tetanii*, *Corynebacterium diphtheriae*, *Haemophilus influenzae*, *Poliovirus* and/or *Hepatitis B virus* comprising administering an effective amount of a multi-component vaccine obtained by the method of claim 27.

37. A method of immunizing a human host against disease caused by infection by *Bordetella pertussis*, *Clostridium tetanii*, *Corynebacterium diphtheriae*, *Haemophilus influenzae*, *Poliovirus*, and/or *Hepatitis B virus*, which method comprises administering to the host an effective amount of a multi-component vaccine obtained by the method of claim 27.

38. The method of claim 36 wherein the host is an infant.

Analysis of *Haemophilus influenzae* Type B Conjugate and Diphtheria-Tetanus-Pertussis Combinati n Vaccines

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Combined vaccines consisting of diphtheria (D), tetanus (T), whole cell pertussis (Pw), and *Haemophilus influenzae* type b (Hib) conjugates are safe and immunogenic; however, there has been a tendency toward lower antibody responses in persons receiving mixtures of DTPw and Hib vaccines. Possible explanations are physical or chemical incompatibilities or immunologic interference. Mixtures of DT–acellular pertussis (Pa) and Hib conjugates have been evaluated as booster vaccinations in children, and preliminary data indicate good safety and acceptable immunogenicity. A study evaluating the combined administration of DTPa, Hib conjugate, and inactivated polio vaccine in infants is ongoing in Finland. Preliminary data suggest that the combination is safe. When the first serum samples were assayed, no major differences in pertussis, diphtheria, and tetanus antibodies were found among children given the vaccines mixed or separately. Hib and polio antibody results are not yet available.

Combined vaccines incorporating diphtheria (D) and tetanus (T) toxoids and pertussis (P) have been available for nearly 50 years. Today they are often administered simultaneously with *Haemophilus influenzae* type b (Hib) conjugate vaccines, which have been used in national vaccination programs over the last decade. Use of Hib conjugates has led to virtual elimination of invasive Hib disease.

The administration of several vaccine antigens simultaneously, either as individual vaccines or mixed in a single product, is accepted as a natural part of all childhood vaccination programs. Public acceptance of new vaccines might be poor if multiple injections were given during a single visit. Thus, to ensure the highest possible compliance and to minimize the cost of vaccine administration, it is reasonable to aim for a combination of vaccine antigens. The next practical step is a DTP-Hib combination vaccine.

Combined vaccines cannot, however, be made by simply mixing vaccines in the same syringe. One must take into consideration all constituents, including stabilizers, preservatives, and adjuvants, and their relative properties and potential chemical and biologic interactions.

DT–Whole Cell Pertussis (Pw)–Hib Combinations

Simultaneous administration of DTPw (i.e., traditional DTP containing Pw) and Hib vaccines is now common for children ages 2–6 months. In the United States, simultaneous administration of DTPw and Hib vaccines increased rapidly after licensure of Hib conjugates, and in 1991, >60% of infants were given Hib concurrently with DTPw [1]. Since then, the percentage has continued to increase. Finnish children have received DTPw and Hib vaccines (PRP-D, HbOC, or PRP-T conjugates) simultaneously since 1986. In 1990–1991, Hib conjugate (PRP-T) was mixed with the DTPw vaccine in at least half of the vaccinations.

DTPw vaccines have been mixed with four available Hib conjugates: PRP-D, HbOC, PRP-OMP, and PRP-T [2–13]. Two ready-made DTPw-Hib combinations (DTPw-HbOC and DTPw–PRP-D) are commercially available in the United States and Canada [14], and one, consisting of DTPw, Hib (PRP-T), and inactivated polio vaccine (IPV), is available in France and four other countries. The US Food and Drug Administration has approved the mixture of DTPw and PRP-T vaccines (lyophilized PRP-T reconstituted with DTPw) t reduce the number of injections in children [15].

Clinical experience with simultaneous use of DTPw and Hib vaccines and of DTPw-Hib combinations is favorable. US data from the Vaccine Adverse Event Reporting System show no signs of potential risks associated with the simultaneous use of US-licensed vaccines [1]. The reactogenicity of the combined vaccines has been acceptable [16]: The frequency of local reactions was only slightly higher than in control groups.

Immunogenicity studies have tested for possible interference between components of DTPw-Hib vaccines. Antibody concentrations in persons receiving mixed vaccines and those receiving vaccines as separate injections have been compared. Results indicate that immune responses in general are somewhat lower in persons receiving combined vaccines than in those given the vaccine components separately (figure 1).

Hib antibody responses seem to be most markedly affected, especially when the PRP-T vaccine (Hib polysaccharide conjugated to tetanus toxoid) is used in the combinations. In four of five studies of DTPw and PRP-T mixtures given at ages 2, 4, and 6 months, Hib antibody concentrations were lower in children who received mixtures than in those given separate injections (geometric mean concentration [GMC] ratios: 0.4–0.9) [3, 10, 11, 12]. In the fifth study, the GMCs were about

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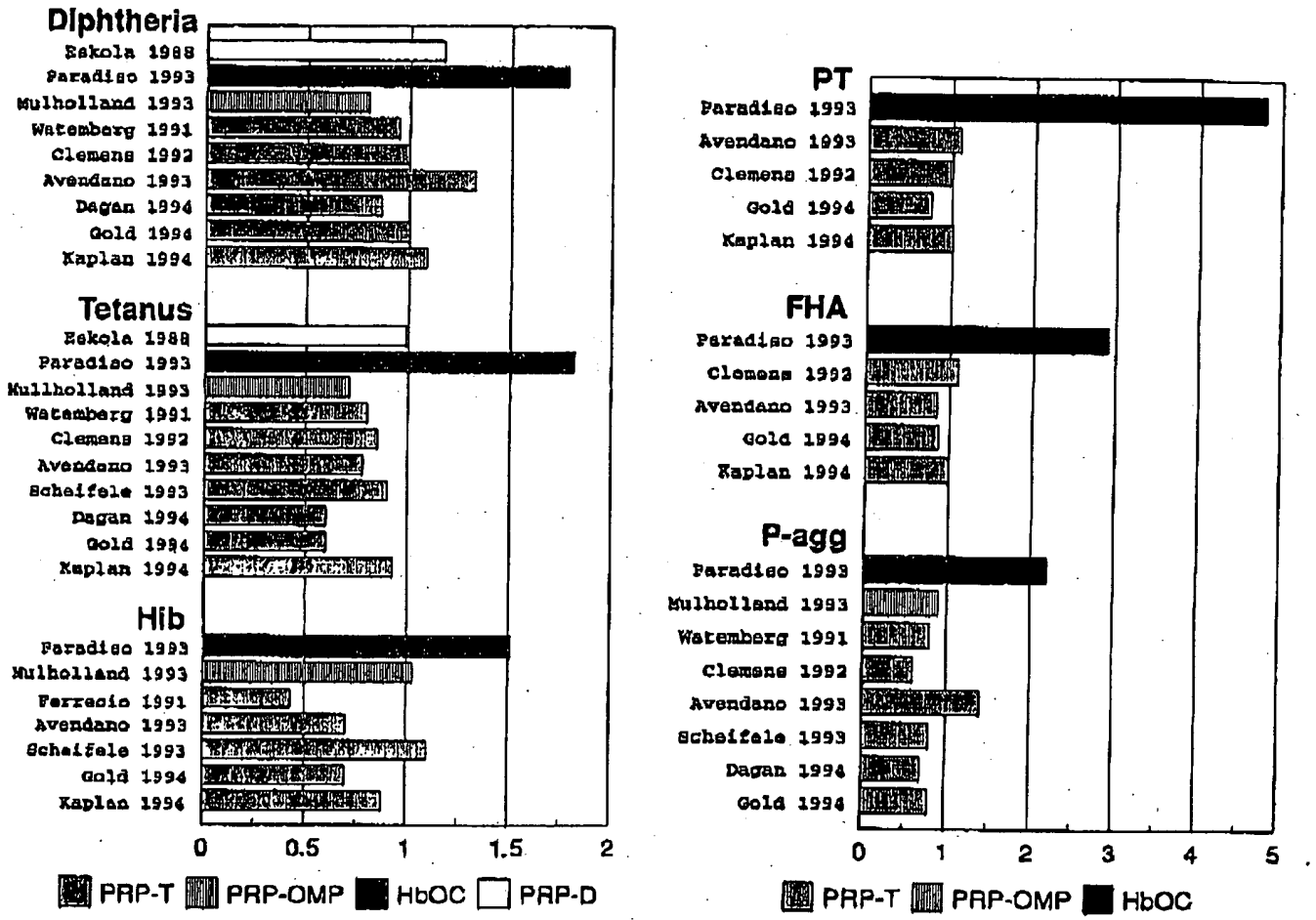

Figure 1. Ratio of geometric mean antibody concentrations of groups receiving diphtheria–tetanus toxoid–whole cell pertussis and Hib vaccines mixed or separately. PT, pertussis toxoid; FHA, filamentous hemagglutinin; P-agg, pertussis agglutinogens.

equal (ratio, 1.1) [7]. However, even in the study with the lowest ratio, the GMCs of Hib antibodies after three doses of vaccine were well above the levels that are generally considered t correlate with protection: 4.80 μg/mL in the combined group and 11.32 μg/mL in children given DTPw and Hib conjugate in separate sites [3]. However, the tendency toward lower antibody responses after DTPw-Hib vaccine administration has not been consistent, and the differences between groups have not always been statistically significant. In one study of the HbOC vaccine [9], the GMCs of Hib, diphtheria, tetanus, and pertussis antibodies were significantly higher in children who received the DTPw and Hib conjugate mixed.

The explanation for the interference is not clear. It is important to recognize that the DTPw vaccines used in these studies differed from each other, as did the Hib conjugate vaccines. In some studies, a tailor-made combination with optimal formulations for each component was prepared; in others, two existing vaccines were mixed before injection. Different preservatives, buffers, and salts and changes in pH might easily affect the immunogenicity of these extemporaneous mixtures. An example of the influence of DTPw vaccine is seen in two studies from Chile [3, 10] in which the study population, vaccination schedule, and Hib conjugate were the same. Only the DTPw vaccines differed. The GMCs of Hib antibodies were 4.80 [3] and 6.94 μg/mL [10] in persons who received the vaccines mixed and 11.32 [3] and 9.93 μg/mL [10] in the groups who received the components separately.

Reasons for the variation might also be immunologic. Prior immunization with free carrier protein has been thought to reduce binding of the conjugate to carrier-specific B cells and to redirect it to polysaccharide-specific B cells, thus leading to better antibody responses. On the other hand, immunization with carrier protein may also expand the number of carrier-specific B cells and direct the conjugate away from polysaccharide-specific B cells. One hypothesis is that antigenic competition and carrier-induced epitopic suppression might occur due

Table 1. Number of children in 3 vaccine study groups with local reactions within 48 h after vaccination.

Reaction	Vaccine study group				
	1 (n = 28)		2 (n = 24)		3 (n = 27)
	DTPa	Hib, IPV	DTPa + Hib	IPV	DTPa + Hib + IPV
At age 4 months					
Redness	1	0	4	3	2
Swelling	1	0	3	0	0
Pain	0	0	2	2	0
At age 6 months					
Redness	6	2	7	3	4
Swelling	2	1	3	1	0
Pain	4	2	3	2	0

NOTE. Data are from forms completed by parents. DTPa, diphtheria–tetanus toxoid–acellular pertussis; Hib, *Haemophilus influenza* type b; IPV, inactivated polio vaccine.

to a local oversaturation of the carrier at the injection site or in local lymph nodes.

Most researchers have concluded that the decline in antibody responses is not clinically important, since Hib, diphtheria, and tetanus antibody concentrations after combined vaccine administration are above the levels generally considered to predict protection, and the pertussis component in the DTPw-Hib vaccine has passed mouse intracerebral challenge studies [17].

DT–Acellular Pertussis (Pa)–Hib Combinations

Pa vaccines were developed in an attempt to reduce the side effects associated with traditional whole cell pertussis vaccination. First results with DTPa-Hib combinations as a booster vaccination are emerging. In two studies, children were primed with DTPw and Hib vaccines and boosted with DTPa-Hib combinations. The mixture of DTPa (containing pertussis toxoid [PT] and filamentous hemagglutinin [FHA] as pertussis antigens) and PRP-D vaccine was well-tolerated by 18-month-old children, and no differences in seroresponses were noted [18]. Another study gives preliminary data of DTPa-HbOC (a pertussis vaccine containing four antigens: PT, FHA, pertactin [PRN], and agglutinogens) given as a booster to toddlers [16]. Diphtheria, tetanus, FHA, PT, and PRN antibodies tended to be higher in children who received the mixed vaccines (GMC ratios, 1.0–1.2), whereas antibodies to the Hib polysaccharide were slightly lower (ratio, 0.8) than in children given the vaccine components as separate injections.

DTPa and PRP-T vaccine combinations are being evaluated in infants. A study on reactogenicity and safety of the combination of DTPa (comprising PT, FHA, and PRN), PRP-T, and IPV (all study vaccines are manufactured by SmithKline Beecham Biologicals, Rixensart, Belgium) in 120 infants is ongoing in Finland. Children receive DTPa alone at age 2 months and DTPa, PRP-T, and IPV, separately or combined at ages 4 and 6 months. Preliminary data suggest that the safety (table 1) and the antibody concentrations to diphtheria, tetanus, and pertussis in the groups receiving the combined vaccines are comparable to those in children receiving the vaccines separately. Figure 2 shows antibody GMCs from the first batch of sera at age 7 months (n = ~20/group). Immune responses to Hib and IPV components will be assayed similarly.

Implications for the Future

In the next few years, data from vaccine trials will affect the development of combined vaccines. Evidence of the protective

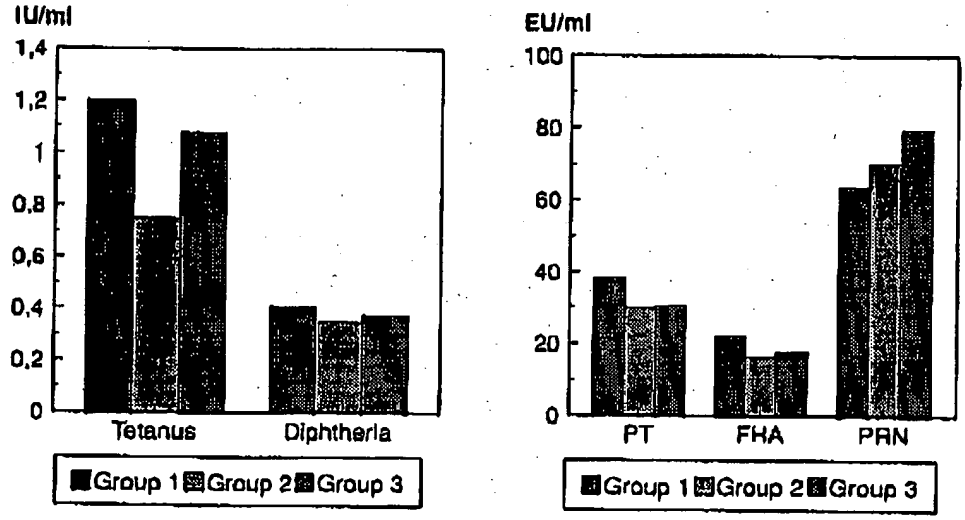

Figure 2. Geometric mean antibody concentrations of diphtheria, tetanus, and pertussis (pertussis toxoid [PT], filamentous hemagglutinin [FHA], and pertactin [PRN]) antibodies in 7-month-old children given diphtheria–tetanus toxoid–acellular pertussis (DTPa) vaccine at age 2 months, and DTPa, PRP-T, and inactivated polio vaccine mixed or separately at ages 4 and 6 months (preliminary data). Group 1, all vaccines separately; group 2, DTPa and Hib vaccines mixed; group 3, all vaccines mixed.

efficacy and clinical usefulness of Pa vaccines will be available soon. National vaccination programs will probably start using DTPa instead of DTPw, and new combined vaccines, such as DTPa-Hib and DTPa-IPV-Hib, may become available.

From experience with DTPw-Hib combinations, one could expect interference between Hib, diphtheria, tetanus, and pertussis antigens in the new DTPa-Hib combined vaccines. The clinical significance of this interference must be considered carefully.

Hib, diphtheria, and tetanus antibody concentrations associated with protection at the population level are known. DTPw-Hib vaccines induce antibody concentrations above these levels and thus are thought to provide protection against disease. However, similar serologic correlates for pertussis are not known. Therefore, to make future evaluation of the combined vaccines practical, ongoing efficacy trials of Pa vaccines must provide clear-cut serologic correlates for protection.

As increasing number of vaccines are recommended for infants, there is need for development of combined vaccines that allow simultaneous administration of several antigens with fewer separate injections. Overall costs would be reduced by eliminating separate vials, packaging, needles, and syringes, by lower storage costs, and by simplifying the vaccination procedure itself. Of more importance, immunization with fewer inoculations and fewer visits may increase the number of children vaccinated, leading to higher compliance and to better vaccination program results.

Note Added in Proof

Final results of the Finnish study described revealed significant interference between the DTPa and Hib conjugate vaccines with impaired Hib antibody responses in the combined vaccine groups (Eskola et al., unpublished data).

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